

## Drug diffusion through cell membrane as a step towards modelling pain relief during anesthesia

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### Abstract

This paper presents an approach to model drug diffusion through a cell membrane as part of a complete model for pain relief during general anesthesia. This model is necessary in order to obtain optimal drug dose for each patient, allowing patient characterization through online identification techniques. By estimating the precise level and/or location of a given drug in the body, control can be improved, leading to a significant reduction in side effects such as over-/under-dosing.

## 1 Introduction

During the last few decades, modern medicine has been influenced by emerging advanced control technologies in various applications such as robotic surgery, electro-physiological life support systems and image-guided therapy and surgery [1]. An important role in today's clinical stage is played by general anesthesia.

Hypnosis, analgesia and neuromuscular blockade of the patient during surgery are cardinal features of general anesthesia. These three main parts of anesthesia can be described as follows: hypnosis which is a general term indicating unconsciousness and absence of post-operative recall of events that occurred during surgery. The level of hypnosis is related with the infusion of the hypnotic drug and can be well characterized by existing models in literature [2]. Muscle relaxation is induced to prevent unwanted movement or muscle tone and causes paralysis during the surgical procedures.

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The muscle relaxants are given intravenously (through the bloodstream) and act directly on the muscles. This part of anesthesia is also relatively well modelled and controlled [3]. Finally, analgesia is an insensibility to pain without loss of consciousness. It is a state in which painful stimuli are not perceived or interpreted as pain and is usually induced by an opioid drug, although trauma or a disease process may produce a general or regional analgesia. This part of anesthesia is lacking insight, models to estimate drug diffusion in the body, dynamics and feedback information for control purposes. Currently, the bottleneck in automated drug delivery systems for anesthesia is the non-availability of an analgesia sensor. Nowadays, indirect measures are used to characterize the analgesic level in the patients (e.g. Ramsay Sedation Score, Analgoscore, vital signs, etc.) [4]. In order to be able to develop a sensor that can measure the analgesic component of general anesthesia, we need to find a model for the diffusion process. Hitherto, there is no model which describes the process of drug diffusion at microscopic level. The role of our paper is thus to make the pioneering steps towards such models for characterizing analgesia.

The first step in inducing analgesia is the drug diffusion into the body, i.e. the anesthetic drug interacts with the central nervous system. Primary targets are the cerebral cortex which controls the perception, and the reticulothalamic system which controls the alertness. An analgesic drug interacts with the central nervous system in order to stop the communication between the nociceptors (i.e. pain stimuli) and the brain, such that pain cannot be perceived anymore. However, this drug needs first to be taken up by the human body, via a complex diffusion process across various cell membranes [5].

Mathematical modeling of drug diffusion can be very useful to better understand the mechanism of drug delivery systems. Therefore, the description of drug transport into the human body can be highly beneficial [6–8] from two points-of-view: (i) allows you to understand the insight of the mechanism and (ii) allows you to do quantitative prediction of the effects of formulation and processing parameters on the resulting drug release kinetics [9]. The major challenge in the development or optimization of automated drug delivery systems is to achieve optimal drug concentration at the site of action. In order to have the optimal concentration-time-profile at the site of action the release of the drug must be controlled as accurately as possible.

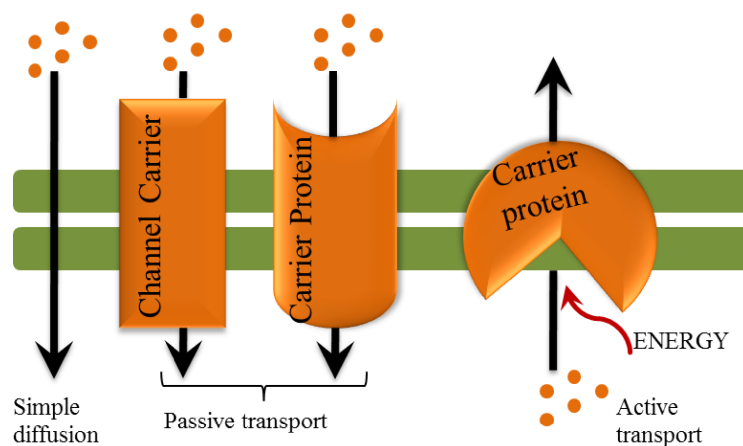
Diffusional behavior is based on the assumption that the molecules perform a random walk in the space that is available to them, this is called Brownian motion [10]. The nature of this random walk is such that the molecules have equal chance to go either way (in the absence of external fields). In its classical form, diffusion is described by Fick’s law and strong experimental evidence of diffusion processes which deviate from this law has been found [11]. Diffusion process represents a very important role in many areas of research, such as: chemistry, biology and physics and the results of this process is to mix and move the molecules from one point to another, which have different concentration gradients.

This paper presents a conceptual study of drug diffusion into the human body which represents a step forward in developing a mathematical model for pain relief (i.e. the development of a pain sensor to control drug release during general anesthesia). The paper has been organized as follows: Section 1 gives an overview of the problem, Section 2 presents the process of drug diffusion through a cell membrane. In Section 3 we present the basic of theoretical modelling of diffusion, while Section 4 presents the preliminary results. Concluding remarks and future work are given in Section 5.

## 2 Diffusion through a cell membrane

Mass transport of molecules in a solution or molecular transport across a barrier is normally measured by fluxes [12]. The flux of a solute is simply defined as the mass or number of molecules moving through a given cross-sectional area during a given period of time. Movement of molecules in solution or molecular transport across barriers can be caused by migration or diffusion. Migration is movement of molecules caused by an external force that is acting on each of the solute molecules. Such external forces can be gravity, electrical fields (in case of charged solutes) or hydrodynamic flow [5].

Diffusion is the random thermal movement of molecules in a solution, and thus diffusion may only cause a net transport of molecules in the presence of a concentration gradient. Generally, diffusion process is characterized as a movement of particles and is rather a physical process than a chemical one. Considering the diffusion in cells, diffusion process is characterized as a form of passive transport where molecules cross the cell membrane (see figure 1). The very important feature of a cell membrane is to serve as a barrier to the outside world, but it has to be mentioned that they are not impenetrable walls [5]. Therefore, we can say that membrane permeability represents a very important role in drug absorption, distribution and elimination. If we consider for example a drug taken orally the target cells are those from the central nervous system. To reach the target drug must cross several membranes: first the barrier presented by the intestinal epithelium, then the walls of the capillaries that perfuse the gut, then the blood-brain barrier. A common feature of all cell membranes is a phospholipid bilayer [13]. Cells absorb molecules and ions from the extracellular fluid, creating a constant in and out flow. The interesting thing about cell membranes is that relative concentrations and phospholipid bilayers prevent essential ions from entering the cell. As shown in figure 1, molecules can diffuse across a membrane down a concentration gradient



**Fig. 1** Several types of molecule movement across membranes.

without the aid of a protein or the input of energy. Passive and active transport require membrane transport proteins. Channel proteins carry out passive transport, but carrier proteins can carry out passive or active transport. Considering all the diffusion processes that occur in the body (passive, active, and facilitated), it is not surprising that the laws governing diffusion are important for

developing and/or optimizing drug delivery systems [8]. In fact, diffusion is important not only in the body but also in some quality control procedures used to determine batch-to-batch uniformity of products. When individual molecules move within a substance, diffusion is said to occur. This may occur as the result of a concentration gradient or by random molecular motion. The most widely used laws of diffusion are known as Fick's first and second laws.

### 3 Theoretical background

Fick's first law [14–16] is used in steady-state diffusion, i.e., when the concentration within the diffusion volume does not change with respect to time ( $J_{in}=J_{out}$ ). In one (spatial) dimension, this is:

$$J = D \frac{\partial c}{\partial x} \quad (1)$$

where:  $J$  is the diffusion flux ( $\text{mol}/\text{m}^2\text{s}$ );  $D$  is the diffusion coefficient ( $\text{m}^2/\text{s}$ );  $c$  is the concentration ( $\text{mol}/\text{m}^3$ ) and  $x$  is the position (m).

The velocity of diffusion is related to the diffusion coefficient of a solute, a constant related to the properties of a given molecule in a given solvent. The diffusion coefficient ( $D$ ) is dependent on the size of the solute molecule and the viscosity of the solvent as described by the Stokes-Einstein equation [17]. In this study we considered the diffusion coefficient to be constant.

Fick's second law is used in non-steady or continually changing state diffusion, i.e., when the concentration within the diffusion volume changes with respect to time ( $t$ ).

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \quad (2)$$

Second law of diffusion can be derived from the first law and mass balance:

$$\frac{\partial c}{\partial t} = -\frac{\partial}{\partial x} J = \frac{\partial}{\partial x} D \frac{\partial c}{\partial x} \quad (3)$$

Assuming the diffusion coefficient  $D$  to be a constant we can exchange the orders of the differentiation and multiplication by the constant:

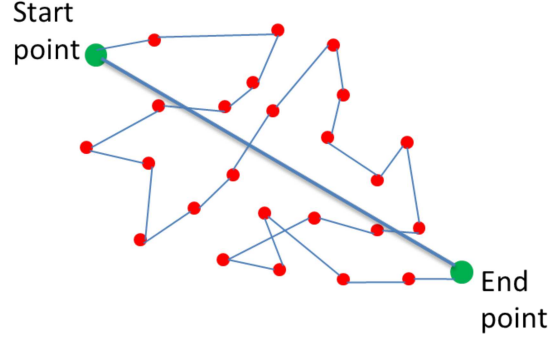
$$\frac{\partial}{\partial x} D \frac{\partial c}{\partial x} = D \frac{\partial}{\partial x} \frac{\partial c}{\partial x} = D \frac{\partial^2 c}{\partial x^2} \quad (4)$$

and, thus, receive the form of the Fick's equations as was stated above.

To study the diffusion of drug into the human body, Fick's law seems to be a very good candidate [14–16]. In this paper we consider the diffusion as a random walk (figure 2) [10]. On microscopic level molecules are in constant random motion which is directly related to the temperature. The laws of kinetic theory of matter dictate the relationship, as a mathematical equation, between molecular motion and temperature. The average kinetic energy of a particle along a given axis is  $kT/2$  where  $T$  is the temperature in degrees Kelvin and  $k$  is the Boltzmann's constant. Let's consider a number of  $N$  particles each of mass  $m$  with velocities  $v_i$ , then the kinetic energy of the system is calculated as follows:

$$\frac{\sum_{i=1}^N mv_i^2/2}{N} = \frac{m}{2N} \sum_{i=1}^n v_i^2 = \frac{mv^2}{2} \quad (5)$$





**Fig. 2** A schematic representation of a random walk of molecules.

where  $v$  is defined as:

$$v = \sqrt{\frac{\sum_{i=1}^N v_i^2}{N}} \quad (6)$$

Therefore,  $\frac{mv^2}{2} = \frac{kT}{2}$  which reduces to:  $v^2 = \frac{kT}{m}$

For our case the numerical solution is obtained based on partial differential equation of diffusion (see equation (2)) and it has the following form:

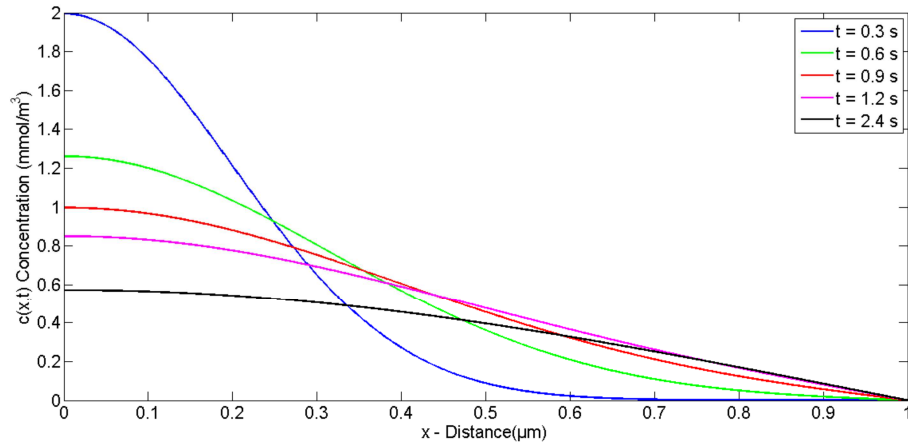
$$c(x,t) = \sum_{N=0}^{\infty} \frac{2}{L} c * \cos \frac{(2N+1)\pi x}{2L} e^{-D[\frac{(2N+1)\pi}{2L}]^2 t} \quad (7)$$

where  $c(x,t)$  is a function of two variables.

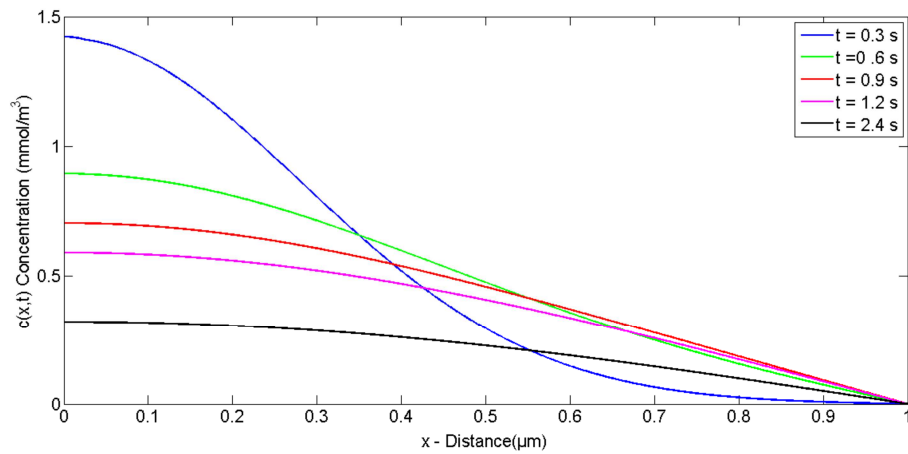
#### 4 Results and discussions

To simulate the drug diffusion across a cell membrane for a certain distance and time we have made two assumptions. First, we consider the simplest model, i.e. the cell membrane is modeled as one layer of thickness  $L$  with a constant diffusion coefficient  $D$  (see figure 3). When considering this assumption means that the cell membrane is a homogeneous layer with constant thickness and diffusivity. This model can be applied to diffusion across a cell membrane under the assumption that the phospholipid bilayer serve as the only barrier to drug diffusion and that it spans the entire cell thickness. The boundary and initial condition for this model are: the diffusion coefficient was estimated to  $D=10^{-10}$  cm<sup>2</sup>/s, the bilayer thickness is approximatively  $1\mu m$ . The concentration at time  $t = 0$  and distance  $x = 0$  is 1 mol/m<sup>3</sup>.

Second assumption is that the model considers a more specific representation of the heterogeneity of the bilayer (see figure 4). The hydrophobic and hydrophilic of the cell membrane were considered to have different diffusion coefficients. Using this approach we are taking into account the variation of diffusivity across the cell membrane, where the hydrophobic layer has a greater diffusion coefficient than the hydrophilic layer. The diffusion coefficient for the hydrophobic layer is  $D_1=10^{-10}$  cm<sup>2</sup>/s and for hydrophilic layer the diffusion coefficient is  $D_2=10^{-6}$  cm<sup>2</sup>/s. The total thickness of the cell membrane was estimated to be about  $1\mu m$ . As in the first case the concentration at time  $t = 0$  and distance  $x = 0$  is 1 mol/m<sup>3</sup>. The results obtained for considering the cell



**Fig. 3** Variation of concentration over thickness of the cell membrane at distinct time points using the first assumption (i.e. one layer).



**Fig. 4** Variation of concentration over thickness of the cell membrane at distinct time points using the second assumption (i.e. two layers).

membrane as being one layer and the second case as being two layers show that when we consider only one layer the decay of concentration is faster than for the case when we consider two layer using the same conditions.

## 5 Conclusion and future work

This paper considered the diffusion process of drug molecules through a cell membrane as initial step towards modelling the analgesia mechanisms. The approach used in this paper has some limitations which will be addressed in the next steps. For instance, the diffusivity of the cell mem-

brane cannot be accurately modeled by a constant due to differences in the cellular structure of the membrane and their contributions to the diffusion. Also in the approach used in this study we did not consider the clearance rate, which quantifies the amount of molecules that diffused from outside the membrane inside the membrane. However, the initial steps undertaken in this paper are necessary to model the diffusion process at microscopic level.

The next step is to tackle the interaction of microscopic and macroscopic levels for characterizing pharmacodynamic profiles of analgesic drugs in the body.

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### References

- [1] J. M. Bailey and W. M. Haddad, Drug dosing control in clinical pharmacology, *IEEE Control Systems Magazine*, 25(2), pp. 35-51, 2005.
- [2] C.F. Minto, T.W. Schnider, Contributions of PK/PD modeling to intravenous anesthesia, *Clinical Pharmacology & Therapeutics*, 84(1), pp. 27-38, 2008.
- [3] T. Mendonca, J.M. Lemos, H. Magalhaes, P. Rocha, S. Esteves, Drug delivery for neuromuscular blockade with supervised multimodel adaptive control, *IEEE Transaction on Control Systems Technology*, 17(6), pp. 1237-1244, 2009.
- [4] T.M Hemmerling, M. Thomas, E. Salhab, G. Aoun, S. Charabati, P.A. Mathieu, The 'Analgoscore': a novel score to monitor intraoperative pain and its use for remifentanyl closed-loop application, *IEEE International conference on systems, man and cybernetics*, pp. 2711-2716, 2007
- [5] O. Steen-Knudsen, Biological membranes. Theory of transport, potential and electric impulses. Cambridge:Cambridge University Press, 2002.
- [6] J. Siepmann, F. Siepmann, Mathematical modeling of drug delivery, *International Journal of Pharmaceutics*, 364, pp. 328 -343, 2008.
- [7] J. Siepmann, A. Goepferich, Mathematical modeling of bioerodible, polymeric drug delivery systems, *Advanced Drug Delivery Review*, 48, pp. 229-247, 2001.
- [8] R. Baker, *Controlled Release of Biologically Active Agents*, John Wiley & Sons, New York, 1987.
- [9] J. Siepmann, F. Lecomte, R. Bodmeier, Diffusion-controlled drug delivery systems: calculation of the required composition to achieve desired release profiles, *Journal of Controlled Release*, 60, pp. 379 -389, 1999.
- [10] H. Berg, *Random Walk in Biology*, Princeton University Press, Princeton NJ, 1993.
- [11] A. Resigno, *Foundations of pharmacokinetics*, Kluwer, New York, 2004.
- [12] S.G. Schultz, *Basic Principles of Membrane Transport*, Cambridge: Cambridge University Press, 1980.
- [13] E. Marieb, K. Hoehn, *Anatomy and Physiology*, Fourth edition, Pearson Benjamin Cummings, pp. 210-215, 2011.
- [14] J. Crank (Ed.), *The Mathematics of Diffusion*, Clarendon J. Pharm. 73 Press, Oxford, pp. 197-208, 1991.
- [15] E.L. Cussler (Ed.), *Diffusion: Mass Transfer in Fluid Systems*, Cambridge University Press, New York, 1984.
- [16] N.A. Peppas, Mathematical modelling of diffusion processes in drug delivery polymeric systems, in: V.F. Smolen, L. Ball (Eds.), *Controlled Drug Bioavailability*, 1, John Wiley & Sons, New York, pp. 203-237, 1984.
- [17] A. Einstein, *Investigations on the Theory of the Brownian Movement*: Dover Publications, Inc.: Mineola, NY, 1956.